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Antibiotic Loaded Acrylic Bone Cement in Orthopaedic Trauma

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1. Introduction

Local antibiotic delivery with antibiotic loaded acrylic bone cement has been used extensively in the management of chronic osteomyelitis and implant related infections. It is considered the gold standard for treatment of musculoskeletal infections (Nelson, 2004; Hanssen, 2005; Samuel et al., 2010). The critical factors in the treatment of any orthopaedic infection are adequate surgical debridement, integrity of the host immune system, and adequate antibiotic levels (Brien et al., 1993). Antibiotic loaded bone cement (ALBC) is popular as it is a proven way to deliver high concentrations of the drug locally, even to avascular areas that are inaccessible by systemic antibiotics. Another advantage of local antibiotic delivery is that the high concentrations of the drug achieved locally would be effective against organisms that are resistant to drug concentrations achieved by systemic antibiotics. Finally, its use results in only low serum antibiotic concentrations and hence less toxicity than that associated with systemic administration. It is perceived that with future developments local antibiotic delivery systems will likely supplant the traditional use of systemic antibiotics for the treatment of musculoskeletal infections (Hanssen, 2005). This chapter will review the role of antibiotic loaded acrylic bone cement in orthopaedic trauma

2. Historical background

The novel concept of local antibiotic delivery by incorporation of gentamicin into acrylic bone cement was introduced by Buchholz et al in the 1970s (Buchholz et al., 1981). Their pioneering work initiated the concept of local drug delivery by antibiotic loaded bone cement thus beginning a new era in the treatment of musculoskeletal infections. One of the first confirmatory laboratory studies was done by Marks et al who showed that Oxacillin, cefazolin, and gentamicin elutes in a microbiologically active form from palacos and Simplex bone cements (Marks et al., 1976). In another early study, Elson et al showed that when antibiotic loaded acrylic bone cement is placed next to cortical bone, dense cortical bone is penetrated by the eluted antibiotic and its concentration in the bone is much higher than that can be achieved safely by systemic administration (Elson et al., 1977). This was followed by in vivo animal studies of Schurman et al and Wahlig et al confirming the elution of pharmacologically active gentamicin from acrylic bone cement (Schurman et al., 1978; Wahlig et al., 1978). Wahlig's report also stated their experience with gentamicin loaded bone cement in forty-one patients with infection of either bone or soft tissue, mainly

of the lower limb. They reported that high concentrations of gentamicin were measurable in the exudate from the wound and that this form of treatment was well tolerated (Wahlig et al., 1978). In 1981, Bucholz published his landmark article on the treatment of infected total joint replacement. Though many orthopaedic surgeons doubted its efficacy till then, his work was well received and established the principle of using antibiotic loaded bone cement (Nelson, 2004; Buchholz et al., 1981).

3. Rationale for use

Musculoskeletal infection presents when bone or orthopaedic implants are colonized by micro-organisms by hematogenous seeding, direct inoculation or airborne contamination (Nelson, 2004). These micro-organisms are planktonic in nature to begin with. Over time and on attachment to implants, they become sessile, reduce their metabolic rate, and become covered by biofilm. Biofilm is an extracellular polymeric glycocalyx. Once formed, this biofilm protects the micro-organism from antimicrobials, opsonization, and phagocytosis (Nelson, 2004). To effectively eliminate bacteria in a biofilm, local antibiotic concentrations achieved must be 10 to 100 times the usual bactericidal concentration. This usually cannot be achieved by safe doses of parenteral antibiotics; therefore, systemic antibiotic treatment of sessile bacterial infections is often ineffective (Nelson, 2004). Antibiotic loaded bone cement is a proven way to deliver high concentrations of the drug locally, particularly in the case of poorly vascularized tissues (Brien et al., 1993; Cerretani et al., 2002; Baleani et al., 2008). Its use also results in a low serum antibiotic concentration and less toxicity than that associated with systemic administration (Cerretani et al., 2002).

Acrylic bone cement was primarily developed as a fixation device for arthroplasty. When used for prosthesis fixation, mechanical properties of the antibiotic loaded acrylic cement need to be considered (Baleani et al., 2008; Persson et al., 2006). Because mechanical performances are not a major concern for spacers or cement beads (they are temporary solutions and in these cases the bone cement is not significantly loaded mechanically), the cement may in these cases can contain high antibiotic concentrations considering only its elution properties, microbiological efficiency, and safety (Baleani et al., 2008).

Sensitivity of bacteria is currently determined on the basis of effective serum levels achievable by systemic antibiotics. Most bacteria defined as resistant by these criteria might be sensitive when exposed to significantly high local tissue levels, as is possible with local antibiotic delivery (Hanssen, 2005; Brien et al., 1993; Hanssen and Spanghehl, 2004). For successful antimicrobial treatment, it is essential to re-classify the etiologic micro-organism as sensitive or resistant based on antibiotic levels locally achievable (Hanssen, 2005; Brien et al., 1993). And so, it has been stressed that the traditional methods of antibiotic sensitivity cannot be extrapolated simply for this method of treatment (Hanssen, 2005). This point is best exemplified by Bucholz's work where the antibiotic placed in the bone cement did not often correlate with the sensitivity of the organisms being treated (Buchholz et al., 1981).

4. Mechanism of action

Elution of antibiotics from PMMA beads follows a biphasic pattern, with an initial rapid phase and a secondary slow phase (Thonse and Conway, 2007). It is now well known that only a small portion of the antibiotic incorporated in bone cement is released. The

mechanism by which these drugs are released is still debated. Early on it was thought that the elution of antibiotics from bone cement, though dependent on many factors, was mainly by diffusion (Buchholz et al., 1984). Bayston and Milner studied the release of gentamicin sulphate, sodium fusidate and diethanolamine fusidate from Palacos and CMW cements. They subscribed to the theory of diffusion of drugs through solid matrices and on the basis of their results, were convinced that antibiotics are released from the cement by a process of diffusion (Bayston and Milner, 1982). The diffusion theory relies on the presence of pores and connecting capillaries in bone cement, through which the circulating medium penetrates and dissolves the incorporated antibiotics which then slowly diffuse outwards (van de Belt et al., 2001). However, others have argued that a critical review of the data they presented does not support this conclusion (Masri et al., 1995).

The most commonly accepted theory is that the elution of antibiotics occurs from the surface of the bone cement and also from the pores and cracks in its matrix (van de Belt et al., 2001; Masri et al., 1995). In support of this theory, elution is improved with increasing surface area and porosity of the cement. Numerous studies have shown that that elution of antibiotics is a surface phenomenon that is related to pores and cracks within the bone cement matrix (Marks et al., 1976; Masri et al., 1995; Wroblewski, 1977; Baker and Greenham, 1988). Van de Belt et al. studied the release of gentamicin as a function of time from six different gentamicin-loaded bone cements and related it to surface roughness, porosity and wettability of the cements. They concluded that the release kinetics of gentamicin from bone cements is controlled by a combination of surface roughness and porosity and suggested that the initial release antibiotic from bone cement was mainly a surface phenomenon, while sustained release over several days was a bulk diffusion phenomenon (van de Belt et al., 2000). This theory best accounts for the biphasic release characteristics of antibiotic bone cement.

5. Ideal antibiotic, dose and bone cement

The ideal local antibiotic delivery system has not been created and the search is still on for both the ideal delivery vehicle and the ideal antibiotic (Nelson, 2004). In most situations today, the use of antibiotic loaded bone cement for treatment of established infection still requires hand-mixing of higher dosages of various antibiotics into bone cement by the treating physician as a clinician directed application (Hanssen, 2005). Self-made antibiotic loaded bone cement beads are cheaper, antibiotic specific and have no availability issues (Samuel et al., 2010).

The traditional attributes for an antibiotic to be acceptable for mixing with bone cement in the operating room are that it must be safe, thermostable, water-soluble, hypoallergenic, bactericidal with a broad spectrum of activity, and in powder form (Brien et al., 1993). There still is no agreement concerning the choice or dose of the antibiotic to be mixed with the cement (Cerretani et al., 2002), as can be seen from the numerous published reports concerning vancomycin (Brien et al., 1993; Cerretani et al., 2002; Baleani et al., 2008), gentamicin, tobramycin (Brien et al., 1993) cephalosporins, clindamycin, ticarcillin, ciprofloxacin, amikacin, meropenem (Baleani et al., 2008), imipenem – cilastin (Cerretani et al., 2002) daptomycin and several others (Hanssen and Spanghehl, 2004). Increasing bacterial resistance against common antibiotics, especially gentamycin, has lead to a demand for alternative drugs (Brien et al., 1993; Baleani et al., 2008; Hanssen and Spanghehl, 2004; Hanssen, 2004).

The optimum dosing of antibiotics in bone cement with regards to safety and efficacy has yet to be determined (Springer et al., 2004). Many authors recommend an antibiotic proportion of 3 to 6% (Buchholz et al., 1981). Higher antibiotic doses are being recommended when the indication is therapeutic, which is the case when acrylic cement is used as beads or spacers (Hanssen and Spanghehl, 2004; Springer et al., 2004). Hanssen classified antibiotic loaded bone cement into high dose (>2 g antibiotic per 40 g of cement) and low dose (<2 g antibiotic per 40 g of cement) and recommended high dose for use as beads or spacers and low dose for prosthesis fixation (Hanssen, 2004). It is possible to introduce as much as 10 to 12 g of antibiotics per 40-gram batch of bone cement and still accomplish cement polymerization. It is postulated that mixing high doses of powdered antibiotics creates considerable cement porosity and facilitates increased elution of antibiotics for at least 4 weeks (Hanssen and Spanghehl, 2004).

The addition of two antibiotics to acrylic bone cement has been shown to increase the elution of the antibiotics (Cerretani et al., 2002; Baleani et al., 2008). Studies have shown that the addition of meropenem increases the elution of Vancomycin (Baleani et al., 2008). This phenomenon has been reported previously for combinations of vancomycin with other antibiotics (Cerretani et al., 2002) and is referred to as passive opportunism (Baleani et al., 2008). The second positive effect of dual antibiotic loaded bone cement is the broadening of antibacterial spectrum (Cerretani et al., 2002; Baleani et al., 2008).

One of the many factors that affect the release of antibiotics from bone cement is the type of cement used (Cerretani et al., 2002; Hanssen, 2004). Palacos cement has been shown to be most effective for the purpose of antibiotic delivery in many studies (Elson et al., 1977; Bayston and Milner, 1982; Wininger and Fass, 1996). Marks et al. proved that, in vitro, Palacos R elutes larger amounts of oxacillin, gentamicin, and cefazolin for a longer period of time than Simplex P bone cement. They showed that scanning electron microscopy studies reveal a larger pore size in Palacos R bone cement compared with Simplex P bone cement. Based on this they concluded that their observation of improved elution with Palacos R bone cement was related to the increased pore size which in turn leads to an increase in the microscopic overall surface area of exposed bone cement (Marks et al., 1976). Increased pore size in palacos cement may be related to the fact that palacos cement contains polymethylmethacrylate as a copolymer 'filler' in contrast with other brands of acrylic bone cement.

6. Drawbacks and adverse effects

The use of antibiotic bone cement results in low serum antibiotic concentrations and hence systemic toxicity is not a significant issue. However, as was stressed in the earlier section, the present trend is to use high doses of antibiotics in beads and spacers when the indication is therapeutic. Springer et al studied the systemic safety and potential adverse effects of using a high-dose antibiotic- impregnated cement spacer after resection arthroplasty of 36 infected total knee replacements in 34 patients. Spacers placed by them contained an average total dose of 10.5 g of vancomycin and 12.5 g of gentamicin and they found that the use of high-dose vancomycin and gentamicin antibiotic spacers seems to be clinically safe (Springer et al., 2004). However, reports do exist in literature where patients have developed systemic toxicity (renal failure) attributable to local antibiotic delivery through bone cement (Dovas et al., 2008; van Raaij et al., 2002; Curtis et al., 2005; Patrick et al., 2006). All

these case reports describe this complication in elderly patients who had been implanted aminoglycoside loaded bone cement. Therefore, though systemic toxicity is uncommon, the use of high dose antibiotic loaded bone cement in elderly patients warrants careful follow-up of renal function.

One of the most common concerns about the clinical efficacy of antibiotic-releasing bone cements is the debate over their role in causing antibiotic resistance in micro-organisms (van de Belt et al., 2001). Like any other biomaterial, PMMA also attracts infectious micro-organisms. These cause the surface of the bio-material to form a micro-ecosystem in which they thrive in a slime-enclosed biofilm. Various in vitro studies have shown the adherence and growth of bacteria on antibiotic-loaded bone cement. As micro-organisms adhere to and grow on these antibiotic-loaded bone cement beads, they are exposed to prolonged periods of low doses of the incorporated antibiotic and eventually become resistant to them (van de Belt et al., 2001; Neut et al., 2003).

Anagnostakos et al. evaluated this problem by bacteriologically examining 18 chains of antibiotic-loaded beads (11 gentamicin-loaded, 7 gentamicin-vancomycin-loaded) that had been implanted for the treatment of orthopedic infections. In 4 cases (3 with *S. epidermidis* and one with MRSA), they found persistence of bacterial growth on the beads. While *S. epidermidis* strains persisted only on gentamicin-loaded beads, MRSA could grow on gentamicin-vancomycin impregnated cement. They observed the emergence of gentamicin-resistant *S. epidermidis* strain in one case despite the fact that preoperative samples of *S. epidermidis* of the patient had been susceptible to the antibiotic. Their study shows that the persistence of bacterial growth on bone cement remains a practical problem and that adherence of bacteria to cement can lead to emergence of bacterial resistance to antibiotics resulting possibly in clinical recurrence of infection (Anagnostakos et al., 2008).

Most of the clinical situations in orthopaedic trauma that require local antibiotic delivery for treatment or prophylaxis of infection also require stimulation of the process of bone regeneration. Classic examples include local antibiotic delivery for prophylaxis of infection in open fractures and treatment of infected non-unions (Thonse and Conway, 2007). There is concern that high concentrations of local antibiotics might affect osteoblast function and subsequent bone regeneration (Hanssen, 2005; Thonse and Conway, 2007). The quinolone class of antibiotics have in particular been shown to have an adverse effect on fracture at the low levels achieved with systemic administration and so it seems that these should be used with caution as systemic therapy or local therapy when bone regeneration is an important aspect of the treatment plan (Hanssen, 2005; Thonse and Conway, 2007). Keeping in mind that a possibility of local toxicity with regard to bone regeneration exists, investigation to determine the ideal dose of locally administered antibiotics to negotiate the balance between eradicating infection without excessively inhibiting the processes of bone regeneration is still required.

One of the main drawbacks of antibiotic bone cement beads is that it requires removal. This means a second surgical intervention solely dedicated for its removal, especially if further procedures are not required for a given case (Hanssen, 2005). The advice to remove antibiotic bone cement beads is based on the possibility that the cement beads would act as a foreign substance suitable for bacterial colonisation after the antibiotic has been depleted (Sener et al., 2010). In practice, after 4 to 6 weeks, beads become surrounded by dense scar tissue and the ability to identify and remove them can become extremely difficult (Hanssen, 2005).

7. Practical considerations

Local antibiotic delivery with antibiotic loaded acrylic bone cement beads has been used extensively in the management of osteomyelitis, infected non-unions and implant related infections (**Fig 1**).



Fig. 1. A 55-year old diabetic male presented to us with fever and painful swelling of left distal femur for a period of 2 weeks. Radiographs at presentation were normal. **(a)**: Tc99m MDP bone scan revealed increased tracer activity in the left distal femur suggestive of osteomyelitis. **(b and c)**: Ultrasonography showed a collection of approximately 50ml around the knee and supra-patellar compartment. Pus culture identified the infecting organism as *Burkholderia pseudomallei*. **(d and e)**: Following decompression and debridement, based on culture sensitivity report, Meropenem loaded acrylic bone cement beads were placed in-situ for local antibiotic delivery. **(f and g)**: Complete clinical resolution of infection was noted and the antibiotic cement beads were removed 12 weeks later. **(h and i)**: However, the patient sustained a pathological fracture of the distal femur following trivial trauma a few months later which necessitated operative stabilisation. The fracture healed well and the patient was infection free at final follow-up 18 months later.

Though newer drug delivery vehicles are being investigated, it remains the most widely used local antibiotic delivery vehicle in orthopaedic surgery. Self- made antibiotic loaded bone cement beads are cheaper, antibiotic specific and have no availability issues (**Fig 2**). However they have been shown to elute less effectively than commercial antibiotic loaded cement beads(Zalavras et al., 2004). In this section, several tips and their rationale for increasing the elution and effectiveness of antibiotic loaded bone cement in clinical practice are discussed.



Fig. 2. Self-made antibiotic loaded bone cement beads strung on braided stainless steel wire.

#1: The liquid monomer is added to methyl- methacrylate powder in an inert bowl with a spatula as per the manufacturer's instructions, and hand mixing is commenced. At the early 'dough' phase, immediately after wetting the cement, antibiotic powder of appropriate weight for the desired concentration is added and thoroughly mixed with the Cement mixture in a standard fashion of one revolution per second to obtain a homogeneous compound.

The usual method advocated for making antibiotic loaded bone cement is mixing the antibiotic powder to the cement powder after which the liquid monomer is added. High volumes of the antibiotic powder make mixing difficult by this method as much of the liquid monomer is lost in dissolving the antibiotic powder. Instead one could first mix the polymethylmethacrylate monomer and cement powder together to form the liquid cement to which the antibiotic powder is added(Samuel et al., 2010).

#2: The choice of the antibiotic is determined by pre-operative culture report if present. Two antibiotics are chosen in the presence of mixed infections. When pre-operative culture reports are unavailable, for the treatment of infection, it is desirable to provide broad spectrum Gram-positive and negative coverage with two antibiotics. I use 2 gm

each of meropenem and vancomycin for a 40 gm batch of bone cement in such situations (total antibiotic concentration: 10%).

Successful therapy depends on achieving high local antibiotic concentrations. Hanssen classified antibiotic loaded bone cement into high dose (> 2 g antibiotic per 40 g of cement) and low dose (< 2 g antibiotic per 40 g of cement) and recommended high dose for use as beads or spacers and low dose for prosthesis fixation (Hanssen, 2004). It is postulated that mixing high doses of powdered antibiotics considerably increases cement porosity and facilitates increased elution of antibiotics (Samuel et al., 2010).

Secondly, the porosity of bone cements depends on the viscosity of the cement, higher viscosity cements possessing a higher porosity than low viscosity ones (van de Belt et al., 2001). I currently use high viscosity CMW1 bone cement to make antibiotic beads. The added advantage of using high-viscosity cement is that it gives a long working time to make the beads. The addition of two antibiotics to acrylic bone cement has been shown to increase the elution of antibiotics possibly by increasing its porosity (Samuel et al., 2010; Cerretani et al., 2002; Baleani et al., 2008). The second positive effect of dual antibiotic loaded bone cement is the broadening of antibacterial spectrum (Cerretani et al., 2002; Baleani et al., 2008).

#3: Prior to mixing of the antibiotic bone cement, two to three strings of braided stainless steel wires are made. These are made by holding a pair of 22 or 24 gauge stainless steel wires with a clamp in one end and a vise in the other end and twisting them in order to braid them.

Removal of antibiotic loaded bone cement after control of infection is desirable. However removal of these beads may be difficult because they are encased in dense fibrous tissue. Many a times, during bead removal, traction is exerted on the stainless steel wires. The use of braided stainless steel wires provides a better hold on the beads when compared to a single smooth stainless steel wire and decreases the chance of the beads from slipping out of the stainless steel wire (Samuel et al., 2010).

#4: The cement beads are made as small as possible (about 8 mm) and strung on to the braided stainless steel wires. It is essential to ensure that adjacent beads have a free gap between each other and are not in contact.

The elution of antibiotics occurs from the surface of the bone cement and also from the pores and cracks in its matrix (Masri et al., 1995). Elution is improved with increasing surface area and porosity of the cement exposed to liquid medium (Masri et al., 1995). Given the time consideration, It is difficult to make symmetrical spheres as advised and the beads end up being more oval. It is more important to ensure that the beads are kept small in size and the beads are so strung on the stainless steel wire that there is a gap between adjacent beads (Masri et al., 1995; Zalavras et al., 2004).

#5: A further attempt to increase the surface area is made by making multiple pits on the surface of the cement beads using a 1.5 mm Kirschner wire as it starts to set.

The use of Kirschner wires to make multiple pits on the surface of the beads to increase the surface area aids better elution of the antibiotic (Samuel et al., 2010).

#6: After setting, the antibiotic beads are placed in vivo. It is desirable to not only be in as close proximity as possible to the focus of infection but to also span it.

Antibiotic loaded acrylic bone cement delivers antibiotics locally but there is not much literature to reveal how far from the beads effective antibiotic levels will be maintained. Though this would depend on the local milieu, it has been suggested that it is no more than 2-3 cm (Samuel et al., 2010). Hence it would seem rational to assume that it is essential to be in as close proximity as possible to the focus of infection and also to span it.

#7: The wound is closed meticulously in layers over a suction drain. This suction drain is however kept closed. The drain is opened every 6 to 8 hours for only 15 minutes to allow periodic drainage of the wound

The antibiotic elutes from the cement beads into the postoperative wound haematoma which acts as a transport medium. The placement of a drain would lead to the removal of collected haematoma and with it the eluted antibiotic and is hence not recommended (Zalavras et al., 2005). Practical considerations however necessitate a drain after debridement. The above method allows the collected haematoma with the eluted antibiotic to act locally before being drained out periodically. Drain removal is done when the drainage level decreases in 48-72 hours as usual.

8. Clinical experience

The use of antibiotic loaded bone cement in orthopaedic trauma can be considered under the following sections:

- Use of antibiotic loaded bone cement for prophylaxis of infection in open fractures.
- Use of antibiotic loaded bone cement for treatment of infected non-unions and osteomyelitis.
- Use of antibiotic loaded bone cement for treatment of infected implants.

8.1 Use of antibiotic loaded bone cement for prophylaxis of infection in open fractures

An open fracture is characterized by soft tissue violation resulting in communication of the fracture site and haematoma with the external environment (Zalavras et al., 2005). Infection is the most dreaded complication of open fractures with higher Gustilo types having a higher incidence of this complication (Zalavras et al., 2005; Ostermann et al., 1995). Microbial growth in open fractures is enhanced by a variety of factors like impaired vascularity, devitalized bone and soft tissue, and loss of skeletal stability (Henry et al., 1993). It is now well recognized that integrity of soft tissue is essential for an uncomplicated course of fracture healing (Henry et al., 1993). Current principles in the management of open fractures include wound irrigation, serial radical debridement, early systemic administration of a short course of broad-spectrum antibiotics, stabilisation of the bone and early soft-tissue coverage (Zalavras et al. 2005; Ostermann et al., 1995). Prevention of infection is one of the main goals of open fracture management. It has been shown that about 65% of patients with open fractures have wound contamination with micro-organisms at the outset (Zalavras et al. 2005). Therefore it can be said that antibiotics are not just for prophylaxis but rather for treatment of wound contamination per se (Zalavras et al. 2005). The use of local antibiotics to achieve therapeutic tissue levels in target areas as an alternative to systemic route which requires high serum levels of potentially toxic and costly antibiotics is an attractive and viable option (Ostermann et al., 1995). Aminoglycosides are the most frequently chosen antibiotic because of their broad anti-bacterial spectrum, thermostability and low

allergenicity(Zalavras et al. 2005). The prophylactic use of local antibiotic delivery has been shown to reduce the risk infection in open fractures(Zalavras et al. 2005; Ostermann et al., 1995; Ostermann et al., 1989).

Ostermann et al described the 'antibiotic bead pouch' technique for the management of severe compound fractures as early as 1989(Ostermann et al., 1989). Their initial report was on the management of 21 type II and III open tibial fractures treated by external fixation augmented by the bead pouch technique. The results of this small series were encouraging with only one deep infection and no case of osteomyelitis. In this technique the patient undergoes a thorough debridement after adequate extension of the wound margins and all avascular, necrotic, and contaminated tissue is removed. This is followed by copious irrigation of the fracture site. A lavage is then performed with normal saline solution and bacitracin solution. The fracture is then reduced and stabilized. In patients with significant soft-tissue injuries in whom closure is not possible at the time of the initial debridement, one or more chains of antibiotic beads are placed in the open wound. A suction drain is brought out through normal intact skin. The soft-tissue defect is covered with an adhesive porous polyethylene wound film (Opsite). This establishes a "closed" bead - hematoma - fracture environment containing high local levels of antibiotic at the fracture site. The drain is used only for overflow purposes and suction is not used. The "bead pouch" dressing and the beads are completely changed every 48 to 72 hours in the operating room under sterile conditions to ensure high levels of antibiotic elution. Wound closure is accomplished by either delayed primary suture closure, split-thickness skin grafts, or flap coverage when further debridements are not required.

The antibiotic bead-pouch technique has numerous advantages. Firstly as expected, high local concentration of antibiotic is achieved in the target area, which is often 10 to 20 times higher than with systemic administration thereby decreasing the need for systemic use of antibiotics and its associated side effects. The most useful indication for this technique is for the management of severe open fractures with Grade III wounds. Secondly, sealing of open fracture site from the external environment by the semipermeable barrier prevents secondary contamination by nosocomial microbes. In this "closed" bead-hematoma-fracture environment, the bone is kept in a moist warm, sterile soft-tissue compartment. This technique facilitates multiple debridements and the dead space is temporarily adequately filled with antibiotic beads extending the available period for soft tissue transfers. In addition, an aerobic wound environment is established which aids in avoiding catastrophic anaerobic infections. The entire process is patient friendly as it avoids frequent painful dressing changes(Henry et al., 1993; Ostermann et al., 1989).

Henry et al reported on the efficacy of antibiotic bead pouch for prophylaxis of deep and soft tissue infection following open fractures. They reviewed 404 open fractures, 334 of which had received bead pouch treatment along with intravenous antibiotics. This group was compared to a historical control of 70 open fractures treated with a protocol of systemic antibiotics alone. The rate of wound infection was 2.7% in the antibiotic bead pouch group as compared to 11.4% in the group treated with antibiotics alone. The rate of chronic osteomyelitis was 2.4% and 14.3%, respectively, in favour of the bead pouch group. They concluded that the antibiotic bead pouch technique was responsible for the reduction of the infection rate. However, there are some concerns with the interpretation of the study results. The wound management protocol in the two groups differed with a

high proportion of the group treated without a bead pouch having immediate wound closure at the time of initial debridement, a practice that probably influences the infection rate(Henry et al., 1990).

In a subsequent study, Henry et al described a consecutive series of 704 compound fractures wherein 227 open fractures in 204 patients were managed with the antibiotic bead pouch technique. Fluid sampled from the bead pouch was shown to contain therapeutic levels of tobramycin with very low serum levels. They reported a wound infection rate of 0% for Grade I open fractures, 1.2% for Grade II compound fractures, and 8.6% for Grade III open fractures. The osteomyelitis rate was 0% in Grade I compound fractures, 2.4% in Grade II open fractures, and 5.5% in Grade III compound fractures. They observed that the bead pouch technique decreased the incidence of infection and permitted a staged wound closure of severe open fractures(Henry et al., 1993).

In another report by the same group, Ostermann et al. compared two groups of open fractures, with 157 receiving prophylactic systemic antibiotics and another group of 547 having antibiotic bead pouch in addition. Comparison of overall infection rates demonstrated a rate of 17% in the group treated with antibiotics alone compared to 4.2% in the bead pouch group. Subdivision of results based on injury severity Gustilo grading revealed statistically significant difference only in grade IIIB injuries. Once again, the wound management protocol between the two groups was not similar raising concerns about the study results. They concluded that the prophylactic use of antibiotic-laden cement beads in addition to systemic antibiotics was of benefit in preventing infectious complications, particularly in Type IIIB open fractures(Ostermann et al., 1993).

In a follow-up landmark article, Ostermann et al described their experience in treating 1085 consecutive compound limb fractures treated in 914 patients(Ostermann et al., 1995). Of these fractures, 240 received only systemic antibiotic prophylaxis and 845 were managed by the supplementary tobramycin loaded bone cement beads. Other therapeutic interventions like copious wound irrigation, meticulous debridement and skeletal stabilisation remained identical in both groups but wound management and the use of antibiotic bone cement beads depended on the surgeon's individual preference and there was no randomisation. In the group treated with local antibiotics 49.5% wounds were primarily closed over beads, 45.1% severe soft-tissue defects were managed by the 'antibiotic-bead-pouch' technique and 5.4% of the wounds were loosely closed over beads as a temporary measure until final wound closure could be achieved. In contrast to the group of patients treated with systemic antibiotics alone which had an overall infection rate of 12% , the infection rate was only 3.7% in the group of patients who were treated with local antibiotic delivery ($p < 0.001$). Both acute infection and local osteomyelitis showed a decreased incidence in the later group which was statistically significant in Gustilo type-IIIB and type-IIIC fractures for acute infection, and in type-II and type-IIIB fractures for chronic osteomyelitis. The drawbacks of the article are that the study was retrospective and the groups were not randomized. The choice of treatment was dependent on the preference of the attending surgeon and the wound treatment was not identical between the two groups with 95% of wounds in the antibiotic bead pouch group being either closed primarily or sealed. Therefore, the relative contribution of the local antibiotic delivery versus the sealing of the wound cannot be determined(Ostermann et al., 1995).

Keating et al studied the efficacy of antibiotic bead pouch in the management of open tibial fractures stabilized by reamed intra-medullary nail. They found that this technique decreased the deep infection rate in open tibial fractures from 16% to 4% in their practice. Though the differences observed did not achieve statistical significance, they suggested that the addition of the bead pouch to the wound management protocol was associated with a worthwhile reduction in deep infection rate(Keating et al., 1996).

Moehring and colleagues compared the efficacy of antibiotic loaded beads with conventional intravenous antibiotics for open fractures in a randomized prospective study(Moehring et al., 2000). The infection rate was lower (5.3%) in the antibiotic bone cement group compared to the conventional systemic antibiotic group (8.3%). However, the study was unable to achieve statistical significance and the data could only suggest that antibiotic bone cement beads are useful in preventing infection in open fractures. The use of local antibiotic delivery with antibiotic loaded acrylic bone cement has now emerged as an efficacious treatment protocol for the prophylaxis of infection in open fractures. However it must be recognized that the question of whether local antibiotics alone is sufficient and systemic antibiotics can be altogether be avoided in these cases is yet to be answered(Ostermann et al., 1995).

8.2 Use of antibiotic loaded bone cement for treatment of infected non-unions and osteomyelitis

Although there are variable definitions, infected nonunion has been defined as a failure of union with persistence of infection at the fracture site for a period of 6 to 8 months(Struijs et al., 2007). The management of this entity is challenging due to the dual problems of controlling infection and providing stability needed for fracture union.(Thonse and Conway, 2007). Treatment protocols may be a single stage revision surgery or a staged strategy where eradication of infection is the primary focus initially and union of the fracture in the later stage(Struijs et al., 2007; Thonse and Conway, 2007). Numerous studies have shown the efficacy of staged strategy using antibiotic bone cement beads for the eradication of infection in infected non-unions though the level of evidence is low. Union rates ranging from 93% to 100% with persistence of infection in 0% to 18% has been reported and is considerably higher than single stage revision surgery or other staged surgery protocols(Struijs et al., 2007; Chan et al., 2000; Ueng et al., 1999, 1997; Ueng et al., 1996). In a randomized controlled trial by Calhoun et al, 4 weeks of intravenous antibiotics was compared with antibiotic beads in 52 patients with infected nonunions having debridement and reconstructive surgery. Patients in the antibiotic bead group also received perioperative (2 to 5 days) systemic antibiotic therapy. The success rate for treating the infection was 83% (20 of 24 patients) in the systemic antibiotic group and 89% (25 of 28 patients) in the antibiotic bead group, suggesting that long-term systemic antibiotic therapy can be substituted by local antibiotic therapy in infected non-unions(Calhoun et al., 1993).

Patzakis et al compared antibiotic loaded bone cement beads (supplemented with as much as 5 days of systemic antibiotics) to systemic antibiotic therapy in 33 patients with chronic osteomyelitis and bone defects. The infection control rate was 100% (12 of 12 patients) in the Septopal group and 95% (20 of 21 patients) in the systemic antibiotic group. Bony union was accomplished in all patients(Patzakis et al., 1993).

The efficacy of local antibiotic therapy has been reported in several clinical studies on open fractures and osteomyelitis. The use of antibiotic bone cement beads for bone and soft tissue defects after debridement for dead space management and local antibiotic delivery is now an accepted treatment protocol especially if reoperation is needed (second-look debridement, soft tissue coverage, bone grafting).

Intra-medullary infections in long bones may be encountered after infection of intra-medullary nails and usually involves the entire medullary canal. These can be difficult to treat with antibiotic cement beads because of difficulties in not only placing but also in retrieving them (Madanagopal et al., 2004). Of late there is considerable interest in the use of antibiotic bone cement coated intra-medullary nails for the treatment of infected non-unions of long bones (Thonse and Conway, 2007; Madanagopal et al., 2004; Shyam et al., 2009). Thonse and Conway described their experience in the management of infected non-unions in a series of 20 patients with a antibiotic cement-coated interlocking intramedullary nail prepared in the operating room (Thonse and Conway, 2007). They achieved the goal of bony union in 85% and infection control in 95% of the patients. However, they noted cement debonding in all the four patients in whom nail removal was done. Shyam et al also reported on their experience with the use of antibiotic impregnated nail for control of infection in cases of infected non-union with bone defect. They prospectively studied 25 cases of infected non-union with varying bone defects and found that this technique was useful for infection control in cases with bone defect <6 cm (Shyam et al., 2009). Antibiotic coated nails not only provide antibiotic delivery but also provide some fracture stability (Madanagopal et al., 2004). It also provides for a more intimate contact with the entire medullary canal and elution of antibiotic to the endosteal surface which is the primary seat of infection in these cases. Though cement debonding and nail breakage may be encountered, these devices are easier to retrieve than traditional cement beads (Madanagopal et al., 2004).

8.3 Use of antibiotic loaded bone cement for treatment of infected implants

Infections in the setting of orthopaedic implants is a particularly serious problem (Sener et al., 2010; Diefenbeck et al., 2006). In orthopaedic trauma, infection of osteosynthetic devices results in considerable morbidity due to prolonged hospitalisation, poor functional status and sepsis. *Staphylococcus aureus* is a common organism that causes deep wound infection after orthopaedic operations and is capable of producing a protective exopolysaccharide biofilm. Other micro-organisms responsible include *Staphylococcus epidermidis*, *Pseudomonas* and other Gram-negative rods (van de Belt et al., 2001). Treatment protocol for this challenging problem is usually a combination of thorough surgical debridement including the removal of necrotic tissue, bone sequestrs and often the implant itself, and local and systemic antibiotic therapy (Diefenbeck et al., 2006).

In addition to surgical considerations, this situation presents a microbiological problem as well. It is recognized that bacteria adhering to implant surfaces change their biological behavior. They produce a biofilm that creates a protective microenvironment against antibiotics (Diefenbeck et al., 2006). More importantly, these micro-organisms reduce their metabolic activity and increase their generation times. As antibiotics act on growing bacteria, the minimum inhibitory concentrations (MIC) of micro-organisms with reduced metabolic activity is increased (Diefenbeck et al., 2006). Systemic antibiotics are ineffective as they cannot reach such a high concentration at the local site. Local antibiotic delivery is therefore a very viable option for this clinical problem, especially if retention of stable implants is planned.

Sener et al studied the effectiveness of antibiotic loaded bone cement in the treatment of implant-related infection in 32 Wistar albino rats in whom deep infection was established after intra- medullary stabilisation of fresh fractures(Sener et al., 2010). They studied the efficacy of three treatment modalities in this randomised study and the 4 treatment groups included: no treatment, surgical débridement, antibiotic-loaded bone cement and antibiotic-loaded autogenous bone. In terms of reduction of microbiological colonies, the antibiotic-loaded bone cement group revealed superior results compared with the other groups. However, they noted that three animals in the bone cement group revealed extensive infection, which was not seen in the debridement only group. Therefore, although antibiotic-loaded bone cement showed superiority over other treatment modalities, they concluded that it should be employed only after unsuccessful trials of débridement because of the risk of extensive infection(Sener et al., 2010). If the infection cannot be eradicated by débridement and the initial rapid phase of antibiotic elution, then the cement beads may provide a suitable environment for the spread of infection and development of resistance to antibiotics(Sener et al., 2010).

9. Recommendations for the antibiotic bone cement for different clinical situations in orthopaedic trauma

9.1 Open fractures where primary wound closure is feasible

In open fractures with contamination, the use of antibiotic loaded bone cement to prevent infection is a viable option (**Fig 3**). Antibiotic beads can be placed in-situ after a thorough debridement and stabilisation of the fracture. The duration of implantation is usually 4-6 weeks and depends on the timing of subsequent planned procedures like bone grafting.



Fig. 3. **(a and b)**: AP and Lateral radiographs of 19-year old man who underwent debridement, intra-medullary nailing for a 24-hour old open contaminated comminuted left femur fracture. Vancomycin and Meropenem loaded acrylic bone cement beads were prophylactically placed in-situ. A bead exchange procedure was done 4 weeks later. **(c and d)**: The beads were removed 6 weeks later. At last follow-up at 12 months, the fracture had united and the patient was free from infection.

9.2 Open fractures where primary wound closure is not feasible

When confronted with a situation of an open fracture where primary wound closure is not feasible, the antibiotic bead pouch technique may be used. This technique allows for dead space management, periodic wound inspection and soft-tissue coverage as an elective procedure.

9.3 Acute infection after plate osteosynthesis

When acute infection complicates plate osteosynthesis, then early surgical intervention can be very successful. The standard procedure for this situation is an exploration of the surgical site, thorough debridement and necrectomy, copious irrigation followed by a course of systemic antibiotics. Local antibiotics with antibiotic loaded acrylic bone cement is extremely useful in this situation. The treatment of early infection by this technique can result in complete eradication of infection when the micro-organisms are still in the planktonic stage. The antibiotic bead chain can be removed during implant removal or bone grafting if the fracture fails to unite. In situations where infection is not cured but only suppressed by the use of antibiotic bone cement beads, radiological evidence of the same will manifest. This situation can be managed by periodic debridement and change of antibiotic bone cement beads with an aim to suppress infection till fracture union. Alternatively if the implant loosens over time, then a spanning fixator to temporarily stabilize the bone till infection is eradicated becomes necessary.

9.4 Infected non-unions

The protocol that can be followed for this situation would be a thorough debridement of all infected tissue, removal of unstable hardware, necrectomy, stabilization of the fracture and antibiotic bone cement beads for local antibiotic delivery. An external fixator is usually used in this situation either for temporary or definitive stabilization of the fracture (**Fig 4**). Local antibiotic delivery with antibiotic bone cement beads has proven to be an effective way to combat these chronic infections. After control of infection, secondary surgical procedures like bone grafting and definitive fracture stabilization may be done as required (**Fig 5**). Widespread intra-medullary infection which usually occurs following an infected intra-medullary nail osteosynthesis is especially amenable to antibiotic bone cement coated intra-medullary nails.

9.5 Chronic osteomyelitis with a stable skeleton

In this situation, a thorough debridement, sequestrectomy and removal of implants if present usually suffices (**Fig 6**). In resistant cases, especially when avascularity of the bone or soft tissue complicates the situation, local antibiotic bone cement beads can be used.

10. Conclusion

The concept of local antibiotic delivery aimed at achieving high concentrations of the drug at target areas, even to avascular areas that are inaccessible by systemic antibiotics, with less toxicity than that associated with systemic administration, is physiologically and economically sound. Since the introduction of this concept by Buchholz et al in the 1970s,

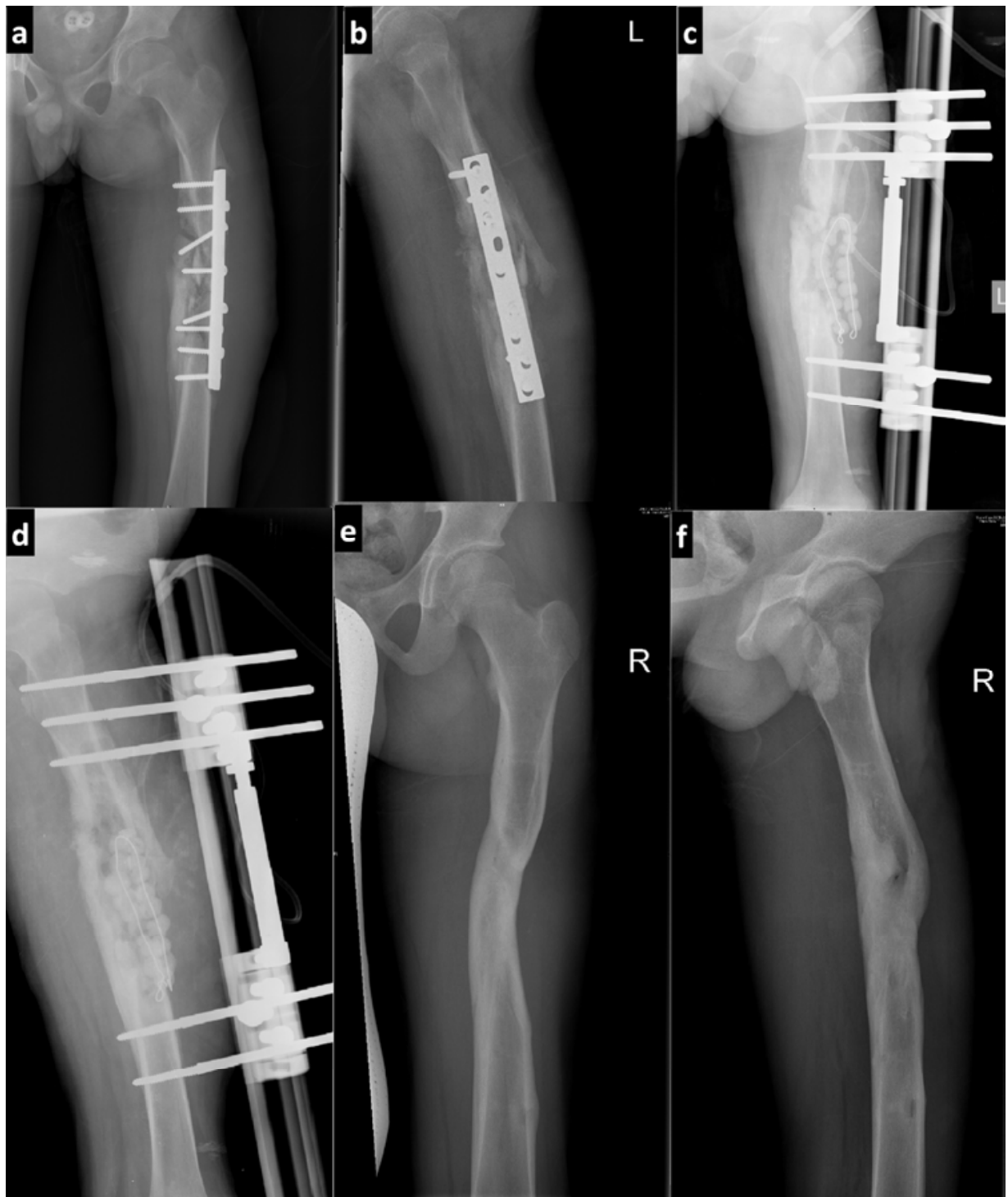


Fig. 4. **(a and b):** AP and Lateral radiographs of a 15-year old boy who presented to us with purulent discharge from his left thigh 8 months following open reduction internal fixation of open left femur fracture. Cultures identified the infecting micro-organism to be Methicillin resistant *Staphylococcus aureus*. **(c and d):** He underwent hardware removal, debridement and fracture stabilisation with a monolateral rail external fixator. Based on culture sensitivity report, Vancomycin loaded acrylic bone cement beads were placed in-situ. **(e and f):** The beads were removed 5 weeks later. At final follow-up 13 months later, the fracture had united and the patient was free from infection.



Fig. 5. **(a and b):** AP and Lateral radiographs of a 34-year old woman who presented to us with infected non-union of the right forearm with broken implants in-situ. **(c and d):** She underwent hardware removal and debridement. Vancomycin and meropenem loaded acrylic bone cement beads were placed in-situ. **(e and f):** 8 weeks later, the beads were removed and the patient underwent open reduction internal fixation of both forearm bones with dynamic compression plates. **(g and h):** At final follow-up 18 months later, the fracture had united and the patient was free of infection.

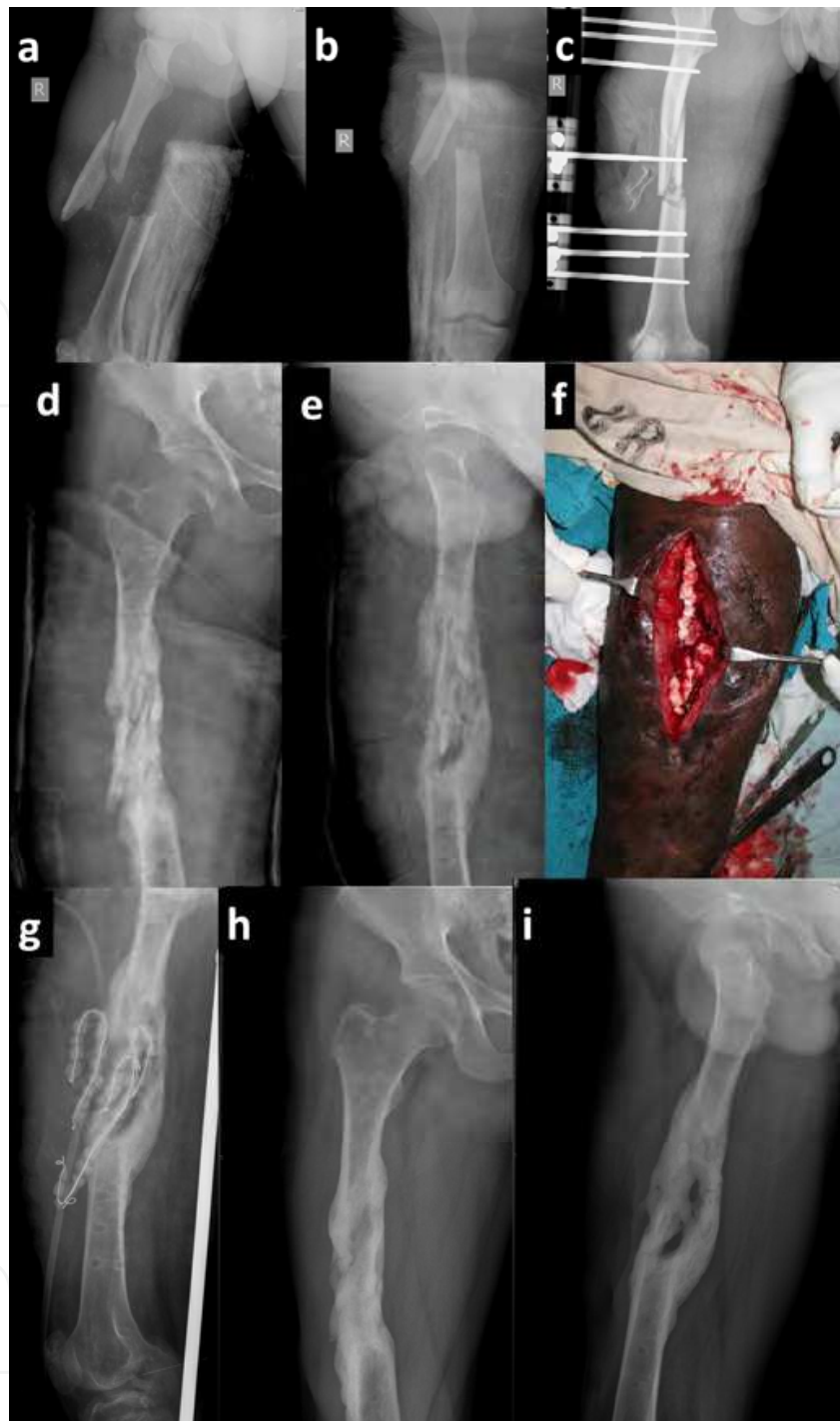


Fig. 6. **(a and b):** AP and Lateral radiographs of a 22-year old male with compound type 3B segmental fracture of the left femur who presented to us 5 days after injury with a contaminated wound. **(c):** After adequate debridement, the fracture was stabilized with a monolateral rail external fixator. **(d and e):** Though the fracture united, the entire middle segment sequestered and the patient developed purulent discharge. The infecting micro-organism was identified to be *Proteus mirabilis* which was multi-drug resistant. **(f and g):** Debridement and removal of the the dead bone was done and the wound was packed with meropenem loaded acrylic bone cement. **(h and i):** At final follow-up 14 months later, the patient was free from infection

antibiotic loaded acrylic bone cement has been used extensively for the prevention and management of orthopaedic infections. Its role in different clinical situations like open fractures, acute and chronic osteomyelitis, infected non-unions and implant related infections has been documented. Though not without drawbacks, it remains the most widely used local drug delivery system in orthopaedics and represents the current gold standard for treatment of musculoskeletal infections. The elution of antibiotic from self-made acrylic bone cement beads, which are cheap, antibiotic specific and have no availability issues, can be improved by attention to detail.

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12. References

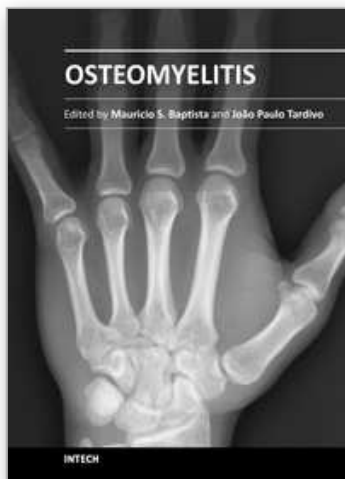
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